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[Intervention Review]

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ABSTRACT

Background

Kidney stones affect people worldwide and have a high rate of recurrence even with treatment. Recurrences are particularly prevalent in people with low urinary citrate levels. These people have a higher incidence of calcium phosphate and calcium oxalate stones. Oral citrate therapy increases the urinary citrate levels, which in turn binds with calcium and inhibits the crystallisation thus reduces stone formation. Despite the widespread use of oral citrate therapy for prevention and treatment of calcium oxalate stones, the evidence to support its clinical efficacy remains uncertain.

Objectives

The objective of this review was to determine the efficacy and adverse events associated with citrate salts for the treatment and prevention of calcium containing kidney stones.

Search methods

We searched the Cochrane Kidney and Transplant Specialised Register to 29 July 2015 through contact with the Trials' Search Co-ordinator using search terms relevant to this review.

Selection criteria

We included randomised controlled trials (RCTs) that assessed the efficacy and adverse events associated with citrate salts for the treatment and prevention of calcium containing kidney stones in adults treated for a minimum of six months.

Data collection and analysis

Two authors assessed studies for inclusion in this review. Data were extracted according to predetermined criteria. Summary estimates of effect were obtained using a random-effects model, and results were expressed as risk ratios (RR) and their 95% confidence intervals (CI) for dichotomous outcomes, and mean difference (MD) and 95% CI for continuous outcomes.

Main results

We included seven studies that included a total of 477 participants, most of whom had oxalate stones. Of these, three studies (247 participants) compared potassium citrate with placebo or no intervention; three (166 participants) compared potassium-sodium citrate with no intervention; and one (64 participants) compared potassium-magnesium citrate with placebo. Overall, quality of the reporting of the included studies was considered moderate to poor, and there was a high risk of attrition bias in two studies.

Compared with placebo or no intervention, citrate therapy significantly reduced the stone size (4 studies, 160 participants: RR 2.35, 95% CI 1.36 to 4.05). New stone formation was significantly lower with citrate therapy compared to control (7 studies, 324 participants: RR 0.26, 95% CI 0.10 to 0.68). The beneficial effect on stone size stability was also evident (4 studies, 160 participants: RR 1.97, 95% CI 1.19 to 3.26). Adverse events were reported in four studies, with the main side effects being upper gastrointestinal disturbance and one patient reported a rash. There were more gastrointestinal adverse events in the citrate group; however this was not significant (4 studies, 271 participants: RR 2.55, 95% CI 0.71 to 9.16). There were significantly more dropouts due to adverse events with citrate therapy compared to control (4 studies, 271 participants: RR 4.45, 95% CI 1.28 to 15.50). The need for retreatment was significantly less with citrate therapy compared to control (2 studies, 157 participants: RR 0.22, 95% CI 0.06 to 0.89).

Authors' conclusions

Citrate salts prevent new stone formation and reduce further stone growth in patients with residual stones that predominantly contain oxalate. The quality of reported literature remains moderate to poor; hence a well-designed statistically powered multi-centre RCT is needed in order to answer relevant questions concerning the efficacy of citrate salts.

PLAIN LANGUAGE SUMMARY

Citrate salts for preventing and treating calcium containing kidney stones in adults

Kidney stones are one of the most common disorders of the urinary tract. They typically affect people aged 40 to 60 years of age and are twice as common in men than women although recent data suggest the risks are more equal. Calcium stones are the most common type of kidney stone and occur in two major forms: calcium oxalate and calcium phosphate. Kidney stones can cause severe abdominal pain and may require urgent treatment; they are one of the main causes of unscheduled admissions in urological practice.

Following treatment even first time stone formers have a risk for recurrence which increased with each subsequent stone. This increased risk of recurrence of stones is mainly attributed to altered composition of urine i.e. low citrate levels. Various prevention strategies including increased fluid intake and oral citrate supplements have been tried to modify the chemical composition of the urine. Citrate therapy is believed to stop crystals from growing into stones. The uncertainty of the true benefit of citrate therapy prompted this review.

We included seven studies (477 participants) in this review. Citrate salts significantly reduce stone size, prevent new stone formation, and results in stone size stability. People experienced more side effects, such as gastrointestinal disturbance, when using citrate salts than when using placebo, however the need for retreatment for stone removal was significantly less with citrate therapy.

BACKGROUND

Description of the condition

Kidney stones (renal stone disease) remain a public health problem around the world irrespective of geographical, cultural or racial backgrounds, with an incidence of approximately 0.1% to 0.3%. The lifetime risk is estimated to be between 10% and 20% in the Western world, but can be as high as 20% to 25% in the Middle East. Stone disease typically affects men two times more commonly than women and peak incidence is in the fourth to sixth decades of life (Magaret 2007; Pak 1998; Sarada 1991). Recent studies reported that the male:female ratio of patients with stones altered from 1.6:1 to 1.2:1 (Nowfar 2011),1.7:1 to 1.3:1 (Scales 2007). Between the mid-1970s and the mid-1990s, the prevalence of stone disease increased from 3.2% to 8.8% in the

USA (Scales 2012; Stamatelou 2003). The stone recurrence rate without treatment is approximately 10% at one year, 33% at five years, 50% at 10 years, and 75% at 20 years (Sutherland 1985; Trinchieri 1999; Uribarri 1989). Following first recurrence, the subsequent relapse risk is increased with a shortened time interval between recurrences (Strauss 1982).

Most stones (60% to 80%) are composed of calcium salts (calcium oxalate, calcium phosphate, or both). The remainder are non-calcium stones such as struvite (5% to 15%), uric acid (5% to 10%), cystine (1%), or other substances (1%) (Miller 2007). Kidney stone formation is based on supersaturation of urinary salts and crystal retention in the urinary tract. Urinary Inhibitors (citrate, pyrophosphate, magnesium, nephrocalcin) and promoters (cell debris, protein aggregates) are involved in the process and deficiency of inhibitors or abundance of promoters in the urine thought to predispose to stone disease (Magaret 2007).

The association of lower urinary citrate with kidney stones was first reported in 1941 (Kissin 1941). Hypocitraturia has been reported in 15% to 63% of patients with kidney stones, presenting either as a single abnormality (10%) or in conjunction with other metabolic disorders (50%) (Zuckerman 2009). Urinary citrate inhibits the crystallisation of calcium salt, levels of less than 1.67 mmol/day (320 mg/day) is defined as hypocitraturia. Severe hypocitraturia is citrate excretion of less than 100 mg/day (0.53 mmol/day) and mild to moderate hypocitraturia is citrate excretion of 100 to 320 mg/day (0.53 to 1.67 mmol/day). These stones are typically composed of calcium phosphate and calcium oxalate. Most people with hypocitraturia are treated with potassium citrate to raise urine citrate levels to reduce the risk of recurrent stone formation.

Minimally invasive techniques including extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotomy (PCNL) and flexible ureteroscopy have transformed the management of stone disease in the last three decades. These newer modalities involve a short hospital stay and, as ESWL can be performed without general anaesthesia, stone treatment, rather than prevention, has become an attractive option for clinicians. However, these interventions cost more to the health care organisations compared to preventive strategies. Preventive measures, which are cost effective, are needed because of the high rate of recurrence (Parks 1996). Metabolic abnormalities are responsible for stone recurrence in 89% to 96% of patients (Levy 1995; Weisinger 1995). A recent study observed a single urine metabolic risk factor in 67% and multiple factors in 27% of patients (Spivacow 2010). Active preventive treatment may be helpful in this group therefore it is desirable to offer specific recurrence preventive measures.

Description of the intervention

Hypocitraturia is recognised as a cause of kidney stone formation. Evidence from non-randomised studies and the European Association of Urology has recommended treatment of hypocitraturia (Turk 2014). The incidence of hypocitraturia varies from 20% to 60% in people who have a propensity to form stones (Nicar 1983; Pak 2003). Hypocitraturia has been observed in 87%, 76% and 40% of people with calcium oxalate, calcium phosphate and uric acid stones respectively (Ratan 2002). The role of citrate preparation has been well documented (Fan 2001; Pak 1991; Pak 1994; Tiselius 1993). Three properties of citrate are considered to help prevent urinary stone formation: (a) urinary citrate acts as an inhibitor of calcium oxalate and calcium phosphate crystal growth and aggregation; (b) citrate alters the ion-activity products of both calcium oxalate and phosphate; and (c) intestinal complex formation between calcium and citrate may reduce calcium excretion. Citrate taken orally is metabolised to bicarbonate in the liver and provides an alkaline load.

There are several citrate containing compounds that have been investigated for the management of stone disease (Allie-Hamdulay 2005; Barcelo 1993; Cicerello 1994; Soygur 2002). The adverse effects of citrate treatment are usually gastrointestinal-related (Mattle 2005). Various citrate formulations, including potassium citrate (Barcelo 1993; Whalley 1996), sodium-potassium citrate (Hofbauer 1994), calcium citrate (Levine 1994), calcium-sodium citrate (Schwille 1997), and potassium-magnesium citrate (Ettinger 1997) have shown to be effective in the treatment and prophylaxis of stone disease. Sodium-potassium citrate in combination with calcium lactate has also been used (Ito 1992).

How the intervention might work

Citrate inhibits the formation of calcium oxalate stones by forming complexes with urinary calcium thereby reducing urinary calcium oxalate saturation. Citrate also inhibits the nucleation, growth, and agglomeration of calcium oxalate crystals (Kok 1986; Meyer 1975).

Why it is important to do this review

Various studies have demonstrated that citrate excretion is significantly lower in stone formers than in normal controls and citrate supplementation increases the urinary citrate level. A number of non-randomised studies have demonstrated a beneficial effect of citrate salts therapy in patients with kidney stones. Preminger 1988 demonstrated superiority of potassium citrate's over sodium-potassium citrate. The European Association of Urology Guidelines on Urolithiasis (Turk 2014) recommends the use of citrate in hypocitraturia. However, the evidence base for this recommendation is limited.

There is no consensus on the best formulation to treat recurrent kidney stone disease. This uncertainty warranted a systematic review to synthesise all available evidence on the efficacy, safety and acceptability of products containing citrate salts to assist people

with stone disease and to reduce recurrence by creating good evidence-based treatment decisions.

OBJECTIVES

The objective of this review was to determine the efficacy and adverse events associated with citrate salts for the treatment and prevention of calcium containing kidney stones.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) that assessed the efficacy and adverse events associated with citrate salts for the treatment and prevention of kidney stones.

Types of participants

Inclusion criteria

- Age: patients aged 16 years or older
- Stone characteristics:
    - Primary or residual kidney stones post ESWL/post ureteroscopic lithotripsy/PCNL, or
    - Active stone formers rendered stone-free following intervention who received citrate therapy for ≥ 6 months.

Exclusion criteria

- Patients with allergies or who are contraindicated to receive citrate salts
- Pregnant women and children with kidney stones
- Kidney impairment (estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m²).

Types of interventions

- Oral citrate therapy administered to treat or prevent kidney stones and compared to placebo or no intervention.
- We assessed only those interventions that had a minimum treatment duration of at least six months.
- Studies comparing citrate salts with other pharmacological interventions for preventing kidney stones were excluded.

Types of outcome measures

Primary outcomes

- Reduction in stone size (reduced residual fragments or complete disappearance) or reduction in stone recurrence rate (new stone formation) documented on plain abdominal radiography or intravenous urography or computerised tomography (CT) at 6, 12 and 24 months after commencement of treatment.
- Stability of stone disease documented on plain abdominal radiography or intravenous urography or CT at 6, 12 and 24 months after commencement of treatment.

Secondary outcomes

- Retreatment rates (retreatment for residual stones) documented during follow-up
- Correction of urinary levels of stone promoters and inhibitors (i.e. alterations in the blood and urine metabolic parameters following treatment)
- Non-compliance with citrate salts
- Serious adverse events and adverse events associated with the intervention (e.g. citrate-related side effects documented during and after therapy).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register (to 29 July 2015) through contact with the Trials Search Coordinator using search terms relevant to this review. The Cochrane Kidney and Transplant Specialised Register contains studies identified from the following sources.

1. Quarterly searches of the Cochrane Central Register of Controlled Trials CENTRAL
2. Weekly searches of MEDLINE OVID SP
3. Hand searching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of hand searched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about the Cochrane Kidney and Transplant.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

A list of titles and abstracts of potentially relevant clinical studies were generated by the search strategy and imported in to bibliographic software (EndNote®). This list was screened by two authors independently and fully published papers were retrieved where appropriate. These papers were further assessed to ensure they met the inclusion criteria of this review and data extraction. Disagreements were resolved by consultation with a third author. We did not impose any language or any other restrictions on any of these searches. Non-English papers were translated where required.

Data extraction and management

Data extraction was carried out independently by the two authors using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one study was noted, only the publication with the most complete data was included. Disagreements were resolved by consensus or referred to a third author. Quality of reporting of the studies was completed independently by one author using the CONSORT 2010 checklist (Schulz 2010). We contacted two authors (Lojanapiwat 2011; Soygur 2002) by email for further data, but unfortunately no responses were received.

Assessment of risk of bias in included studies

Risk of bias was independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2). Data were also assessed according to the method of randomisation, allocation concealment, adequate descriptions of numbers, and reasons for patient withdrawal, as detailed in the Cochrane Handbook for Systematic Review of Interventions (Higgins 2011).

Measures of treatment effect

For dichotomous outcomes (success, effectiveness, re-treatment, and serious adverse effects) results are expressed as risk ratios (RR) with 95% confidence intervals (CI). Where continuous scales of measurement are used to assess the effects of treatment (mean procedure time), the mean difference (MD) is used, or the standardised mean difference (SMD) if different scales were used.

Unit of analysis issues

The first period of cross-over studies was to be included.

Assessment of heterogeneity

Heterogeneity was analysed using a Chi² test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I² test (Higgins 2003). I² values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

RESULTS

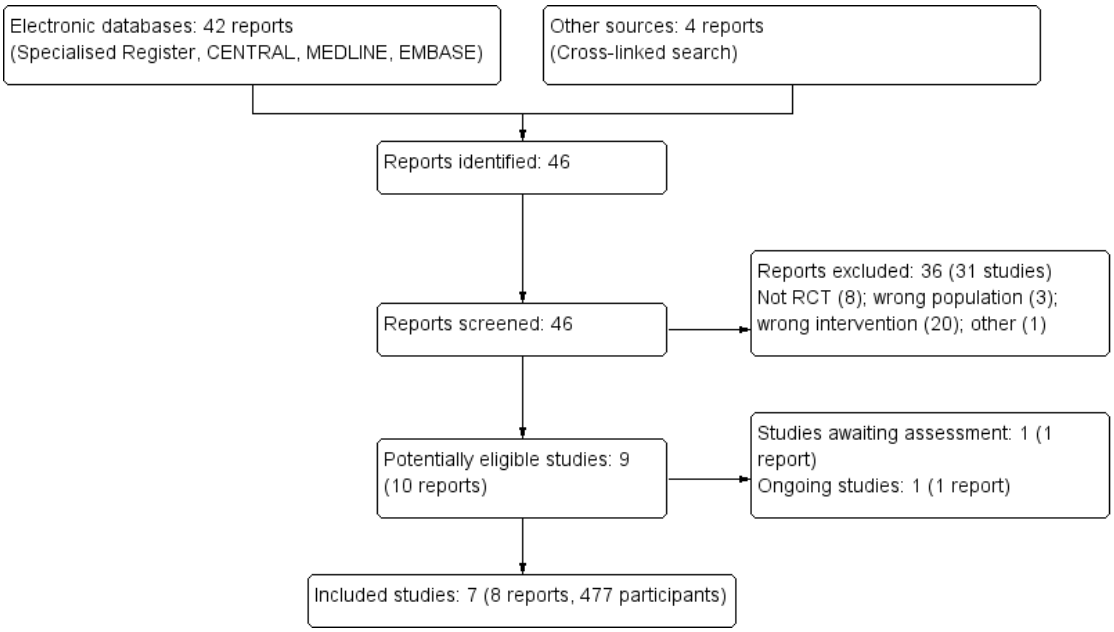
Description of studies

See: Characteristics of included studies and Characteristics of excluded studies.

Results of the search

Forty reports were retrieved as identified in the Cochrane Kidney and Transplant Specialised Register and further four reports were retrieved via a cross-link search. These 44 reports were screened (titles, abstracts and full-text) and seven studies (eight reports) fulfilled our inclusion criteria (see Figure 1).

Figure 1. Flow diagram showing article selection process



Prior to publication of this review a final search of the Specialised Register identified one new potential study (Krishna Reddy 2014) and one ongoing study (NCT01754779) and these will be assessed for inclusion in a future update of this review.

Included studies

The primary objective for all studies (Barcelo 1993; Cicerello 1994; Ettinger 1997; Hofbauer 1994; Jimenez Verdejo 2001; Lojanapiwat 2011; Soygur 2002) was to demonstrate the efficacy of citrate salts in reducing the number of stone episodes from a population of known stone formers. Urinary citrate levels before and after treatment was a secondary outcome measure in five studies (Cicerello 1994; Ettinger 1997; Hofbauer 1994; Jimenez Verdejo 2001; Lojanapiwat 2011).

Design

All studies were RCTs and participants received a minimum of six months treatment. Three studies had a follow-up period of 12 months (Cicerello 1994; Lojanapiwat 2011; Soygur 2002). Three studies reported 36 months follow-up (Barcelo 1993; Ettinger 1997; Hofbauer 1994) and one study reported 48 months follow-up (Jimenez Verdejo 2001).

Sample sizes

These seven studies reported the results for 477 participants. One hundred and sixty one participants had residual stones < 5 mm post ESWL/PCNL; the remaining 316 participants were stone-free at the start of the study but were active stone formers.

Setting

Five studies were conducted at a university teaching hospital (Ettinger 1997; Hofbauer 1994; Jimenez Verdejo 2001; Lojanapiwat 2011; Soygur 2002); one study was conducted at a general hospital with university links (Cicerello 1994) and one study was conducted at a private hospital with university links (Barcelo 1993).

Participants

Selection criteria varied among included studies.

- Ettinger 1997 included patients with two or more calculi within the previous five years and at least one calculus within the year prior to recruitment.
- Barcelo 1993 selected patients with moderately severe active urolithiasis (two or more stones formed during the previous two years composed of calcium oxalate or a mixture of calcium oxalate and calcium phosphate) with low or low normal urinary citrate.
- Hofbauer 1994 recruited patients with recurrent idiopathic calcium oxalate urolithiasis (at least one stone over the previous three years).

- Lojanapiwat 2011 studied patients who were stone-free or had residual stones < 4 mm following ESWL or PCNL.
- Soygur 2002 and Jimenez Verdejo 2001 enrolled post shock wave lithotripsy (SWL) patients who were either stone-free or residual stones of < 5 mm or < 2 mm respectively.
- Cicerello 1994 recruited patients with residual fragments < 5 mm post ESWL as well as patients with struvite stones, the struvite stone patients were excluded from analysis in this review.

Interventions

Three studies used potassium citrate (Barcelo 1993; Jimenez Verdejo 2001; Soygur 2002), three studies used potassium-sodium citrate (Cicerello 1994; Hofbauer 1994; Lojanapiwat 2011) and one study used potassium-magnesium citrate (Ettinger 1997) therapy. Dietary advice was given to both placebo and treatment arms of all the studies. No study made use of the same dosing regimen and length of follow-up differed between the studies.

Outcomes

Among the seven included RCTs, five (Barcelo 1993; Ettinger 1997; Hofbauer 1994; Lojanapiwat 2011; Soygur 2002) reported participants' demographic characteristics; Jimenez Verdejo 2001 did not report any participants' demographic details. All studies reported outcomes with regard to new stone formation, and four studies (Cicerello 1994; Jimenez Verdejo 2001; Lojanapiwat 2011; Soygur 2002) reported on stone stability and reduction in stone size. Urinary parameters at the end of study were reported by four studies (Cicerello 1994; Ettinger 1997; Jimenez Verdejo 2001; Lojanapiwat 2011).

Excluded studies

See: Characteristics of excluded studies.

After initial database search 32 studies (36 reports) which were found were subsequently considered ineligible. Eight were excluded because they were not randomised (Jaipakdee 2004; Kato 2004; Khanniazi 1993; Koff 2007; Lee 1999; Pearle 2002; Preminger 1988; Sakhaee 1983). The remaining 24 studies were RCTs that investigated interventions for kidney stones that did not meet our inclusion criteria.

- Three studies (Gao 2010; Sarica 2006a; Schell-Feith 2006) had patient population age of less than 16 years of age.
- Fourteen studies (Allie-Hamdulay 2005; Aras 2008; Brardi 2012; El-Gamal 2012; He 2004a; Heguilen 2005; Mechlin 2011; Pinheiro 2013; Sakhaee 1983; Schell-Feith 2006; See 2012; Singh 2011a; Tosukhowong 2008; Zerwekh 2007) had less than six months citrate therapy.
- In four studies (Ettinger 1976; Fernandez Rodriguez 2001; LIMONE Study 2012; Mortensen 1986) a different intervention was used. i.e. potassium acid phosphate, thiazide, citric acid.
- Two studies (Premgamone 2001; Singh 2012) citrate was used in the control group (i.e. no control arm).
- One study (Pak 1992) assessed only biochemical parameters.

Risk of bias in included studies

In general the risk of bias of the included studies as judged by the authors was low (Figure 2; Figure 3). However there were no reported power calculations for sample size in any of the included studies. Baseline demographics were reported in all studies apart from Jimenez Verdejo 2001. Comparison of baseline demographics was reported by Ettinger 1997. Soygur 2002 and Cicerello 1994 minimised the patient variables by randomising to matched groups. The differences in baseline biochemistry between two groups were reported by Ettinger 1997 as not significant. In four of the included studies, baseline urinary citrate was comparable (Barcelo 1993; Cicerello 1994; Jimenez Verdejo 2001; Soygur 2002).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

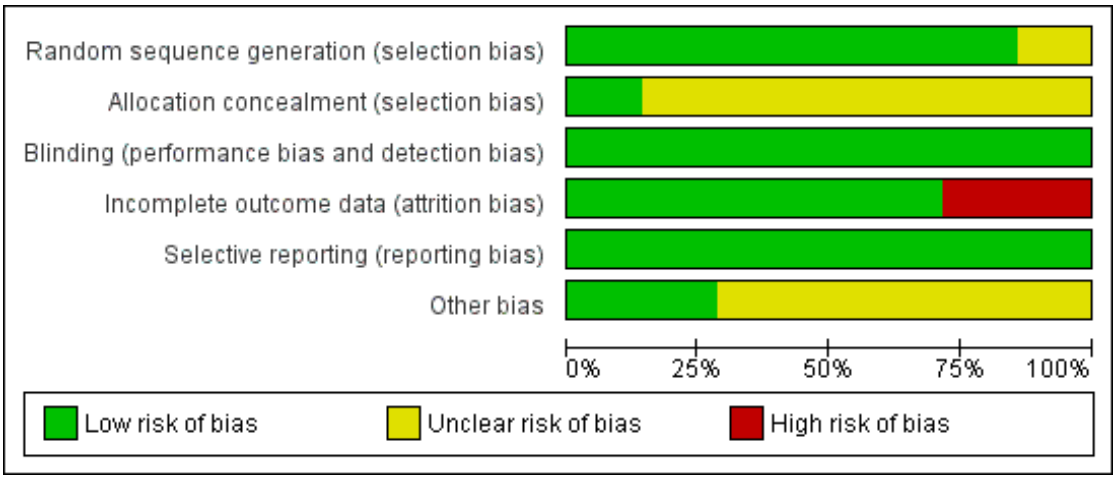
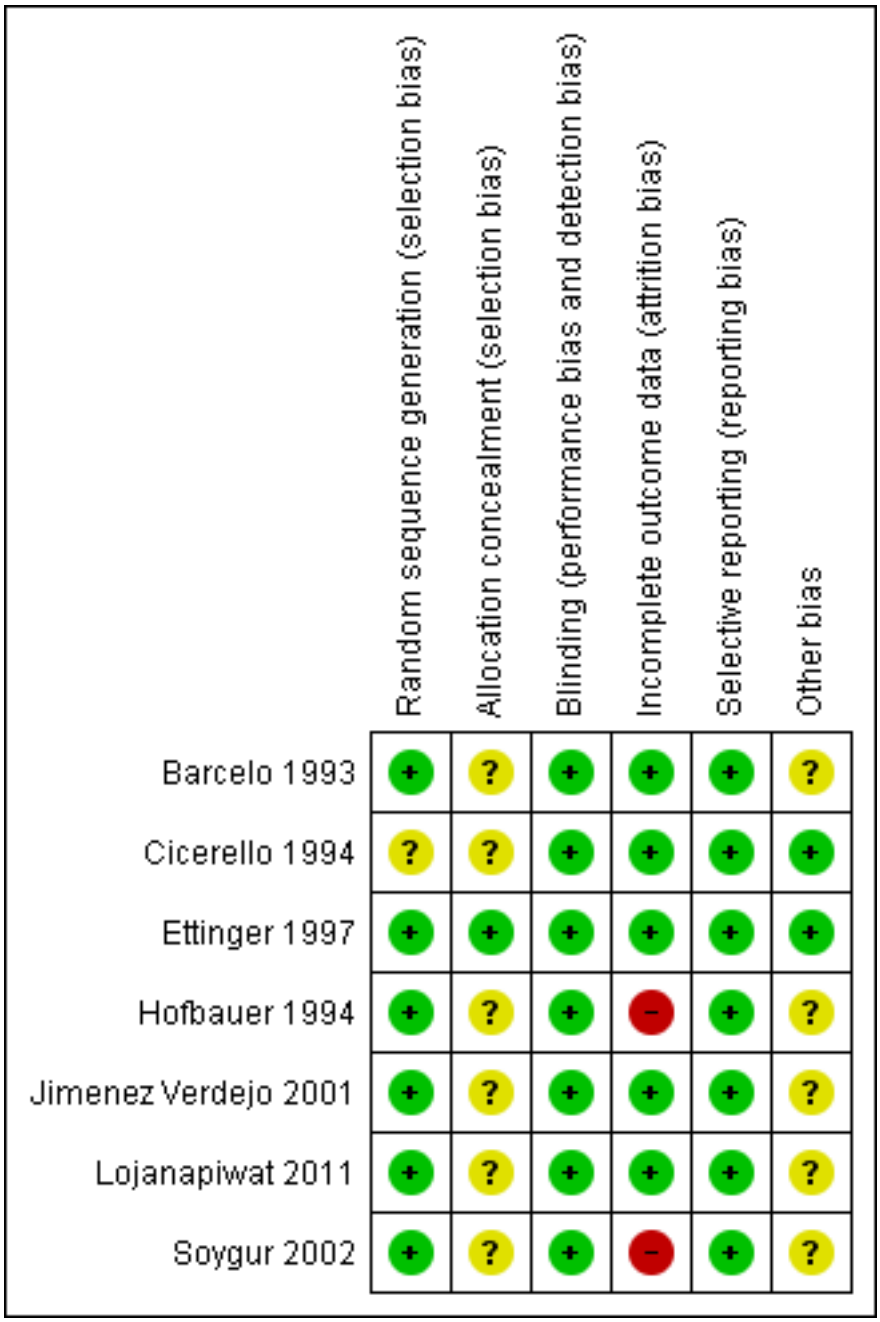


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Minimisation of confounding variables was ensured by Soygur 2002 and Cicerello 1994 by randomising participants by age, sex and urinary biochemical markers, no other studies reported how participant variables were minimised prior to allocation.

Blinding

Two studies were reported as double-blind RCTs (Barcelo 1993; Ettinger 1997). Ettinger 1997 described blinding of an outcome assessor who reviewed the X-ray films, and Cicerello 1994 reported the radiologist who reviewed the interval imaging was unaware of the study protocol.

Incomplete outcome data

In five studies the number of participants randomised matched the number reported in the results ().

- Barcelo 1993 excluded dropouts from the main analysis but did report outcomes of five non-compliant participants with continued follow-up. No interim results were reported for 11 participants who dropped out due to non-compliance.
- Soygur 2002 did not report results in 20/110 participants who were enrolled in the study, they described randomisation of 90 participants and these are included in the results. They later report 20 dropouts, of whom six dropped out due to epigastric discomfort. We have therefore presumed that all 110 were enrolled and randomised but results for the 90 completing the study are reported.
- Lojanapiwat 2011 enrolled 80 participants; results were reported for 76, no explanation was provided about which group the dropouts belonged to.

Other potential sources of bias

Barcelo 1993 reported a difference in the dosing regimen from the study protocol dosing regimen. The participants allocated to the treatment arm were to take 60 mEq/day of potassium citrate however average consumption was 45 mEq/day and participants taking less than 30 mEq/day were excluded. Unfortunately the final results do not specify which dosing regimen was most effective in stone prevention.

Effects of interventions

Reduction in stone size

Four studies (Jimenez Verdejo 2001; Lojanapiwat 2011; Soygur 2002; Cicerello 1994) assessed the role of citrate therapy for reducing stone size. Citrate therapy significantly reduced stone size compared to control (Analysis 1.1 (4 studies, 160 participants): RR 2.35, 95% CI 1.36 to 4.05; I^2 = 4%).

New stone formation

All studies reported new stone formation, with follow-up ranging from 12 to 48 months. Citrate therapy significantly reduced the incidence of new stone growth compared to control (Analysis 1.2 (7 studies, 324 participants): RR 0.26, 95% CI 0.10 to 0.68; I^2 = 80%). The high heterogeneity can be attributed to Hofbauer 1994. However when this study was removed from the meta-analysis there was no change to either the direction or significance of the result (6 studies, 286 participants): RR 0.24, 95% CI 0.15 to 0.41; I^2 = 0%).

Stone size stability

Four studies (Jimenez Verdejo 2001; Lojanapiwat 2011; Soygur 2002; Cicerello 1994) reported stone size stability. Citrate therapy was significantly beneficial in preventing stone growth compared to the control group (Analysis 1.3 (4 studies, 160 participants): RR 1.97, 95% CI 1.19 to 3.26; I^2 = 0%).

Urinary citrate levels

Three studies reported urinary citrate levels at the end of the study (Cicerello 1994; Ettinger 1997; Lojanapiwat 2011). Urinary citrate was significantly higher in the treatment group compared to the control group (Analysis 1.4 (3 studies, 179 participants): MD 192.77 mg/d, 95% CI 108.19 to 277.35; I^2 = 43%). Jimenez Verdejo 2001 reported urinary citrate levels at the end of study which were considerably higher than baseline, however standard deviations were not provided and therefore these results were excluded from the meta-analysis.

Adverse events

Four studies reported adverse events which included upper gastrointestinal disturbance (stomach pains, bloating, nausea) and rash (Barcelo 1993; Ettinger 1997; Hofbauer 1994; Jimenez Verdejo 2001). There were more gastrointestinal adverse events in the citrate group, however this was not significant (Analysis 1.5.1 (4 studies, 271 participants): RR 2.55, 95% CI 0.71 to 9.16; I^2 = 45%). Ettinger 1997 reported no significance in rash (Analysis 1.5.2 (64 participants): RR 3.19, 95% CI 0.13 to 75.43). Ettinger 1997 also reported 11.5% of participants complained of diarrhoea (with one participant reporting multiple episodes), however the actual number involved was unclear and therefore was excluded from meta-analysis (Table 1).

Dropouts

All studies reported dropouts due to non-compliance. Lojanapiwat 2011 and Soygur 2002 only reported the total number of dropouts and therefore could not be included in the meta-analysis. There was no significant difference in dropouts due non-compliance between citrate therapy and control (Analysis 1.6.1 (5 studies, 311 participants): RR 1.20, 95% CI 0.72 to 1.99; I^2 = 0%).

Five studies reported dropouts due to adverse events (Barcelo 1993; Ettinger 1997; Hofbauer 1994; Jimenez Verdejo 2001; Soygur 2002). Soygur 2002 only reported the total number of dropouts due to epigastric discomfort (6 participants) and therefore could not be included in the meta-analysis. There were significantly more dropouts with citrate therapy compared to control (Analysis 1.6.2 (4 studies, 271 participants): RR 4.45, 95% CI 1.28 to 15.50; I^2 = 0%) (Table 1).

Retreatment

Two studies reported the need for retreatment (Barcelo 1993; Jimenez Verdejo 2001). The need for retreatment was significantly less with citrate therapy compared to control (Analysis 1.7 (2 studies, 157 participants): RR 0.22, 95% CI 0.06 to 0.89; I^2 = 41%) (Table 1).

DISCUSSION

Summary of main results

Citrate salts are an effective intervention in the treatment and prevention of kidney stones. The evidence from seven RCTs included in this review has demonstrated good efficacy with citrate therapy compared to control (placebo, usual care). However, this review was unable to demonstrate the most effective type and dose of citrate salt needed to achieve this clinical benefit. The precise duration of treatment remains to be defined. Interestingly, dropout rate due to side effects is low.

Overall completeness and applicability of evidence

We conducted a comprehensive search of the databases and included the non-English language literature. Two review authors independently assessed the material to minimise errors, and a third author was consulted to resolve any disputes. During the initial part of review process, we excluded the RCT by Cicerello 1994 as it did not meet our inclusion criteria of patients aged 18 year or more. However, it was felt that this is an important study and accordingly our initial inclusion criteria was altered to include patients over 16 years of age. We attempted to contact two authors for further clarification of data without success. The included studies were assessed for reporting completeness by using the CONSORT 2010 checklist (Schulz 2010) however, we took into consideration that six studies were published prior to these guidelines (Barcelo 1993; Cicerello 1994; Ettinger 1997; Hofbauer 1994; Jimenez Verdejo 2001; Soygur 2002). The two double-blind studies (Barcelo 1993; Ettinger 1997) were reported more thoroughly than the non-blinded studies.

This review included studies reporting on citrate supplements either for the treatment or prophylaxis of calcium containing kidney stones. Four studies (Cicerello 1994; Jimenez Verdejo 2001; Lojanapiwat 2011; Soygur 2002) analysed the effect of citrate salts in post-treatment group (either post-ESWL or post-PCNL) with residual stones and were able to demonstrate a significant benefit of citrate therapy in stone size reduction and stone size stability. Overall, evidence for specific citrate treatment is limited due to use of different citrate salts at varying dosage, varying follow-up periods, and varying follow-up imaging protocols. Despite significant benefit of citrate salts in prevention and treatment of kidney stones these limitations, make it difficult to recommend a specific salt in day-to-day practice.

Quality of the evidence

The seven RCTs included in this review have used different citrate salts at varying doses. Length of follow-up also varied between the studies. Power calculations have not been reported by any of the studies. Barcelo 1993 and Ettinger 1997 are double-blind and have a good description of blinding; however the overall description of study methodology by Barcelo 1993 was poor as assessed by the CONSORT 2010 checklist (Schulz 2010). The level of heterogeneity reported for outcomes assessing treatment of stone disease was low, but this was not the case when analysis was carried out on new stone formation where the level was high: I^2 = 80%, and was attributed to Hofbauer 1994. A moderate-strength evidence (RR, 0.25, 95% CI 0.14 to 0.44) was observed in a recent review (Fink 2012).

Studies with over 12 months follow-up took serial X-rays at six-monthly intervals (Barcelo 1993; Ettinger 1997; Hofbauer 1994; Jimenez Verdejo 2001). Interestingly, the individual data for stone growth or new stone formation at various intervals has not been reported in any of the studies. It is therefore impossible to comment on the exact time where change in the stone size did occur and hence optimal duration of therapy cannot be defined. In three studies (Cicerello 1994; Lojanapiwat 2011; Soygur 2002) with up to 12 months follow-up, new stone formation varied from 0% to 8% in the treatment arm and 29% to 42% in the control arm. Among studies that reported > 12 months follow-up (Barcelo 1993; Ettinger 1997; Hofbauer 1994; Jimenez Verdejo 2001), the percentage of patients with new stones varied from 8% to 69% in the treatment arm and 44% to 73% in the control arm. Interestingly, Hofbauer 1994 was the only study that failed to demon-

strate any difference in new stone formation between treatment and control arms. this study utilised a method of altering the dose of citrate to maintain urine pH at 7.2. This was considerably more alkaline than reported by the other studies which reported pH of 6.29 to 6.64. Eleven of 16 participants in the treatment arm reported new stone formation; only one of these was reported as a calcium phosphate stone. Authors failed to report on the number of stones analysed in the laboratory, therefore, it could be postulated that the high pH may have attributed to more calcium phosphate stone formation although the crystal inhibitory effect of citrate due to the presence of high citrate levels in the urine should counterbalance the pH effect on calcium phosphate saturation. Another explanation could be the higher intake of sodium increased calcium excretion and therefore promoted new stone formation.

Potential biases in the review process

The quality of the included RCTs was moderate to poor which can reduce the reliability of the estimates of the effectiveness of citrate salts. We attempted to improve reliability by contacting two authors for missing data however we were unsuccessful in obtaining any further details.

Agreements and disagreements with other studies or reviews

Fink 2012 produced a comprehensive systematic review on the medical management to prevent recurrent nephrolithiasis this included the use of citrate salts. Their findings compliment ours. Pearle 1999 described the use of citrate salts in a meta-analysis on treatment options for calcium oxalate stones. There was insufficient evidence at the time to analyse the effects of this treatment and reported insufficient evidence.

AUTHORS' CONCLUSIONS

Implications for practice

Citrate salts are currently in use for the treatment and prevention of calcium-containing kidney stones, this review has highlighted the evidence that there is some beneficial effect of prescribing this medicine particularly to prevent new stone formation. The administration of citrate salts has been shown to increase excretion of citrate in the urine. Which citrate salt is most favourable remains an unanswered question. While there were more adverse events reported with citrate therapy, this was not significant. These findings must be considered in the context of moderate to poor study design and incomplete outcome reporting. Consideration also needs to be made to the economic value of prescribing citrate salts in the long-term; this is one area which has not been addressed.

Implications for research

This review highlights the lack of good quality reported literature in the use of citrate salts for kidney stone management. A multicentre study which compares different citrate salts in patients who are stone-free, recurrent stone formers or have residual fragments < 4 mm to placebo is required. The primary outcomes should be new stone formation, stone growth, visits to the emergency department, proven renal colic or intervention for stones. Alterations in the urinary parameters should be included as secondary outcomes. A complete metabolic work up according to European guidelines at baseline, and six monthly thereafter should be considered. Gold standard CT KUB should be used for assessment allowing all types of stones to be studied. The study should incorporate interval reporting at 6, 12 and 24 months so evidence can be gathered on the long term benefits of using citrate salts. Adverse events should be reported thoroughly and specify if patients dropped out due to an event. Future studies should report on the health economics of citrate salts in preventing new stone formation after interventions (ESWL, PCNL and ureteroscopy) and their impact on the growth of residual fragments.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Barcelo 1993

Methods	• Study design: double-blind parallel RCT • Study duration: 3 years • Duration of follow-up: 3 years
Participants	• Country: Spain • Setting: single centre (private hospital with university link) • Adults with severe active lithiasis (2 or more stones formed during the previous 2 years prior to recruitment) composed of calcium oxalate or a mixture of calcium oxalate and calcium phosphate with an isolated hypocitraturia abnormality ○ Baseline pH: treatment group (5.4 ± 0.5); control group (not reported) ○ Baseline citrate (nmol/d): treatment group (1.9 ± 0.5); control group (not reported) ○ Baseline calcium (mg/d): not reported • Number (randomised/analysed): treatment group (28/18); control group (29/20) • Mean age ± SD: 44 ± 11 years • Sex (M/F): treatment group (8/10); control group (9/11) • Exclusion criteria: hypercalciuria; hyperuricosuria; hyperoxaluria; diabetes; kidney failure; hyperkalaemia; active UTI; gastrointestinal disease; patients with three or more stones in the same kidney
Interventions	Treatment group • Potassium citrate: 20 mEq (4 tablets) 3 times/d Control group • Identical placebo: 4 tablets 3 times/d Both groups advised to increase fluid intake to 2 to 3 L/d plus reduce sodium intake
Outcomes	Outcome measures • X-ray, blood and urine analyses were taken at baseline and 6 monthly intervals Outcome definitions • Stone growth represented an increase of more than 100% in stone size as seen on the X-ray • New stone formation represented spontaneous passage in the absence of pre-existing stones, stone passage without any change in the number of stones, appearance of new stones on the X-ray or newly formed stones requiring ESWL or surgical removal
Notes	• Average tablet consumption was 9/d, non-compliance set at tablet consumption of ≤ 6 tablets/d • End of treatment citrate not reported for control group • Dropouts excluded from study analysis • Funding: Ferrer Pharma International S.A. Barcelona Spain supplied the potassium citrate and placebo
Risk of bias	

Barcelo 1993 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly allocated into two groups
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and investigators blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes (of interest to this review) were reported
Other bias	Unclear risk	Average tablet consumption was 9/d, no evidence of the range, those < 6 were excluded

Cicerello 1994

Methods	• Study design: parallel RCT • Study duration: 12 months • Duration of follow-up: 12 months
Participants	• Setting: Private hospital with university link • Country: Italy • Adults with 2 to 5 residual stones none more than 5 mm on X-ray 6 weeks after ESWL; calcium oxalate stones (40); stones with infection (30) ○ Baseline pH: not reported ○ Baseline citrate (mg/d): treatment group (408.1 ± 137.5); control group (415.3 ± 160.8) ○ Baseline calcium (mg/d): treatment group (194.6 ± 108.7); control group (198.3 ± 91.3) • Number (randomised/analysed): treatment group (20/20); control group (20/19) • Mean age ± SD: 42 ± 17 years • Gender: Male 37; females 33 • Exclusion criteria: > 5 stones and stone size > 5 mm
Interventions	Treatment group • Sodium-potassium citrate: 6 to 8 g/d in 3 divided doses for 12 months • Advised fluid intake to achieve a daily urine output of more than 2.5 L and to avoid dietary excess • The infective stone formers were given full dose antibiotics for 10 d/mo Control group • Advised fluid intake to achieve a daily urine output of more than 2.5 L and to avoid dietary excess

Cicerello 1994 (*Continued*)

	• The infective stone formers were given full dose antibiotics for 10 d/mo
Outcomes	• X-ray: 6 and 12 months • Kidney ultrasound • Urine culture and sensitivity • 24 h urine calcium, sodium, potassium • Excretory urography at 12 months • Citrate level in urine • Urine pH Outcome definitions • Stone clearance, stone growth, stone re-aggregation
Notes	• Infective stone formers were excluded from this review • Dropouts excluded from study analysis • Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding but outcome unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes (of interest to this review) were reported
Other bias	Low risk	The study appears to be free from other sources of bias

Ettinger 1997

Methods	• Study design: double-blind parallel RCT • Study duration: 36 months • Duration of follow-up: 37 months
Participants	• Country: USA • Setting: university teaching hospital • Adults with calculi containing at least 50% or more calcium oxalate; two or more calculi within 5 years and 1 calculus within past 2 years; no secondary cause for

Ettinger 1997 (*Continued*)

	nephrolithiasis ○ Baseline pH: treatment group (6.01 ± 0.46); control group (5.96 ± 0.41) ○ Baseline citrate (mg/d): treatment group (587 ± 374); control group (549 ± 280) ○ Baseline calcium (mg/d): treatment group (237 ± 120); control group (275 ± 131) • Number: treatment group (31); control group (33) • Mean age ± SD (years): treatment group (48.6 ± 11); control group (47.5 ± 9) • Sex (M/F): treatment group (22/9); control group (28/5) • Exclusion criteria: obstructive uropathy; chronic urosepsis; kidney failure (Cr 1.8 mg/dL or more); RTA; ESWL within last six months
Interventions	Treatment group • 42 mEq potassium, 21 mEq magnesium and 63 mEq citrate per day. Divided into 2 tablets 3 times/d for 36 months Control group: • Two placebo tablets 3 times/d for 36 months Both groups: dietary advice: restricted salt, refined sugar, oxalate rich foods, animal protein but allowed up to two servings of dairy food/d
Outcomes	• Coned view of X-ray of kidneys at baseline,12, 24, 36 months • 24 h urine metabolic screening (SMA-24) at baseline, 5, 9, 13, 17, 21, 25, 29, 33, 37 months Outcome definitions • Stone clearance and radiographic appearance of new calculi, or passage of new stones
Notes	• Dropouts excluded from study analysis • Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Patients were stratified according to presence of stone or stone-free status and both groups received visually identical tablets
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data

Ettinger 1997 (*Continued*)

Selective reporting (reporting bias)	Low risk	Pre-specified outcomes (of interest to this review) were reported
Other bias	Low risk	The study appears to be free from other sources of bias

Hofbauer 1994

Methods	• Study design: parallel RCT • Study duration: 36 months • Duration of follow-up: 36 months

Participants	• Country: Austria
	• Setting: University teaching hospital
	• Active stone formers with at least 1 stone annually over previous 3 years
	  ○ Baseline pH: not reported
	  ○ Baseline hypocitraturia: treatment group (18/25); control group (16/25)
	  ○ Baseline hypercalciuria: treatment group (12/25); control group (10/25)
	• Number: treatment group (25); control group (25)
	• Mean age ± SD (years): treatment group (55 ± 11.2); control group (54.8 ± 14.7)
	• Sex (M/F): treatment group (15/10); control group (16/9)
	• Exclusion criteria: primary hyperparathyroidism; RTA (type 1); UTI; hypercalcaemia or diseases of the gastrointestinal tract

Interventions	Treatment group • Sodium-potassium citrate initially 10 g, 3 times/d thereafter individually adapted to obtain a mean urinary pH of 7.0 to 7.2 Control group • General prophylactic instructions i.e. abundant liquid intake and dietary restrictions
Outcomes	• X-ray and kidney USS of kidneys at 6-monthly intervals • 24 h urine collections and serum monitoring 6-monthly Outcome definitions • New stone formation
Notes	• Dropouts excluded from study analysis • Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomly divided into two groups
Allocation concealment (selection bias)	Unclear risk	Not reported

Hofbauer 1994 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding but outcome unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Large number of dropouts especially in the treatment group (36%)
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes (of interest to this review) were reported
Other bias	Unclear risk	Insufficient information to permit judgement

Jimenez Verdejo 2001

Methods	• Study design: parallel RCT • Study duration: 48 months • Duration of follow-up: 48 months
Participants	• Country: Spain • Setting: university teaching hospital • Adults post ESWL with calcium oxalate or calcium phosphate stones, those with residual stones were ≤ 2 mm ○ Baseline pH: treatment group (5.97); control group (6.01) ○ Baseline citrate (mg/d): treatment group (548.3); control group (539.4) ○ Baseline calcium (mg/d): treatment group (206.2); control group (253.4) • Number (without stones/with residual stones): treatment group (25/25); control group (25/25) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: metabolic disease, recurrent UTI, Cr ≥1.5 mg/dL; congestive heart failure; hyperkalaemia; metabolic alkalosis; active gastroduodenal ulcer; intestinal obstruction; pregnancy or lactation; treatment with diuretics, captopril, indomethacin; baking sodium or other preparations containing potassium and thiazide or allopurinol treatment
Interventions	Treatment group • Potassium citrate 40 mEq/d in granular form, divided into two doses Control group • General advice of high fluid intake
Outcomes	• X-ray at baseline three and six months then six monthly thereafter Outcome definitions • Change in residual stone size, new stone formation
Notes	• Funding: not reported
Risk of bias	

Jimenez Verdejo 2001 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised into groups
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Not blinded but outcome unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes (of interest to this review) were reported
Other bias	Unclear risk	Insufficient information to permit judgement

Lojanapiwat 2011

Methods	• Study design: parallel RCT • Study duration: 12 months • Duration of follow-up: 12 months
Participants	• Country: Thailand • Setting: university teaching hospital • Kidney stones ≤ 4 mm at 8 weeks after ESWL/PCNL; all patients had calcium stones on infrared spectroscopy ○ Baseline pH: treatment group (5.8 ± 0.77); control group (5.7 ± 0.66) ○ Baseline citrate (mg/d): treatment group (259.2 ± 214.7); control group (304.3 ± 233.8) ○ Baseline hypocitraturia: treatment group (4/39); control group (7/37) • Number (stone-free/residual stones): treatment group (13/26); control group (26/11) • Mean age ± SD (stone-free/residual stones): treatment group (48.8 ± 8.26/49.1 ± 12.04); control group (54.1 ± 10.12/45.9 ± 8.93) • Sex (M/F): treatment group (26/13); control group (26/11) • Exclusion criteria: UTI; anatomical abnormality; clinical history of urological surgery
Interventions	Treatment group • Potassium-sodium citrate: 81 mEq/d (27 mEq, 3 times/d). • Dietary advice to have high fluid intake throughout the study. Control group • Dietary advice to have high fluid intake throughout the study

Lojanapiwat 2011 (*Continued*)

Outcomes	• X-ray at baseline and 12 months • Serum chemistry and urinalysis at six and 12 months • Evidence of spontaneous stone passage Outcome definitions • New stones determined by spontaneous passage in absence of pre-existing stones and/or appearance of new stones on X-ray
Notes	• Contacted author via email for further clarification of results, no reply obtained • Dropouts excluded from study analysis • Funding: Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Independently block randomised
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding but outcome unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes (of interest to this review) were reported
Other bias	Unclear risk	Insufficient information to permit judgement

Soygur 2002

Methods	• Study design: parallel RCT • Study duration: 12 months • Duration of follow-up: 12 months
Participants	• Country: Turkey • Setting: university teaching hospital • Kidney stones < 5 mm on abdominal X-ray/USS 4 weeks after ESWL; all patients had calcium oxalate stones without infection ○ Baseline pH: not reported ○ Baseline hypocitraturia: treatment group (20/46); control group (14/44) ○ Baseline hypercalciuria: treatment group (6/46); control group (12/44) • Number (stone-free/residual fragment): treatment group (28/18); control group (28/16)

Soygur 2002 (*Continued*)

	• Mean age, years (stone-free/residual fragment): treatment group (44.6/40.6); control group (37.2/42.5) • Sex (M/F): treatment group (32/14); control group (16/30) • Exclusion criteria: UTI; anatomic abnormality of urinary tract; history of urologic surgery or urolithiasis; definite metabolic disease (hyperparathyroidism or RTA)
Interventions	Treatment group • Potassium citrate: 60 mEq/d divided into 3 doses • Dietary advice: high fluid intake to achieve a urine output of 2 L/d, avoid oxalate foods and restriction of meat products to 8 oz/d Control group • Dietary advice: high fluid intake to achieve a urine output of 2 L/d, avoid oxalate foods and restriction of meat products to 8 oz/d
Outcomes	• X-ray and USS of kidneys at 12 months • Urine citrate levels at 12 months Outcome definitions • New stone formation • Stone growth defined as increment of > 2 mm on X-ray
Notes	• Contacted author via email for further clarification of results, no reply obtained • End of study hypocitraturia not reported for control group. • End of study hypercalciuria not reported for either treatment of control group • Dropouts excluded from study analysis • Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Independently block randomised
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Not blinded but outcome unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	110 participants were enrolled onto the study but only 90 randomised - no baseline data given for those not randomised
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes (of interest to this review) were reported
Other bias	Unclear risk	Insufficient information to permit judgement

Cr- creatinine; ESWL - extracorporeal shock wave lithotripsy; M/F - male/female; PCNL - percutaneous nephrolithotomy; RCT - randomised controlled trial; RTA - renal tubular acidosis; USS - ultrasound scan; UTI - urinary tract infection

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Allie-Hamdulay 2005	RCT; treatment only for 7 days; no follow-up imaging
Aras 2008	RCT; treatment only for 3 months; no follow-up imaging
Brardi 2012	RCT; treatment only for 5 months.
El-Gamal 2012	RCT; for ureteral calculi and only 4 weeks of treatment
Ettinger 1976	RCT; wrong intervention (potassium acid phosphate)
Fernandez Rodriguez 2001	RCT; wrong intervention (thiazide therapy)
Gao 2010	RCT in children; no follow-up imaging
He 2004a	RCT; only 4 weeks of treatment; no radiology
Heguilen 2005	RCT; treatment only for 45 days; no follow-up imaging
Jaipakdee 2004	Non-RCT
Kato 2004	Non-RCT
Khanniazi 1993	Non-RCT
Koff 2007	Non-RCT
Lee 1999	Non-RCT
LIMONE Study 2012	RCT; wrong intervention (citric acid rather than citrate salts)
Mechlin 2011	RCT; stone recurrence was not an outcome; treatment for 3 days; no follow-up imaging
Mortensen 1986	RCT; wrong intervention (thiazide treatment)
Pak 1992	RCT; only biochemical parameter outcomes
Pearle 2002	Non-RCT
Pinheiro 2013	RCT; only 3 days of treatment

(*Continued*)

Premgamone 2001	RCT; citrate as control no placebo arm
Preminger 1988	Non-RCT
Sakhaee 1983	RCT; healthy post-menopausal women, treatment for 2 weeks
Sakhaee 2004	Non-RCT
Sarica 2006a	RCT in children
Schell-Feith 2006	RCT in neonates; less than 6 months treatment
See 2012	RCT; treatment only for 6 weeks
Singh 2010	RCT; citrate as control no placebo arm
Singh 2011a	RCT; treatment only for 12 weeks
Singh 2012	RCT; citrate as control no placebo arm
Tosukhowong 2008	RCT, treatment only for 3 months; no follow-up imaging
Zerwekh 2007	RCT; healthy adults with 5 weeks bed rest

RCT - randomised controlled trial

DATA AND ANALYSES

Comparison 1. Citrate salts versus placebo or no intervention

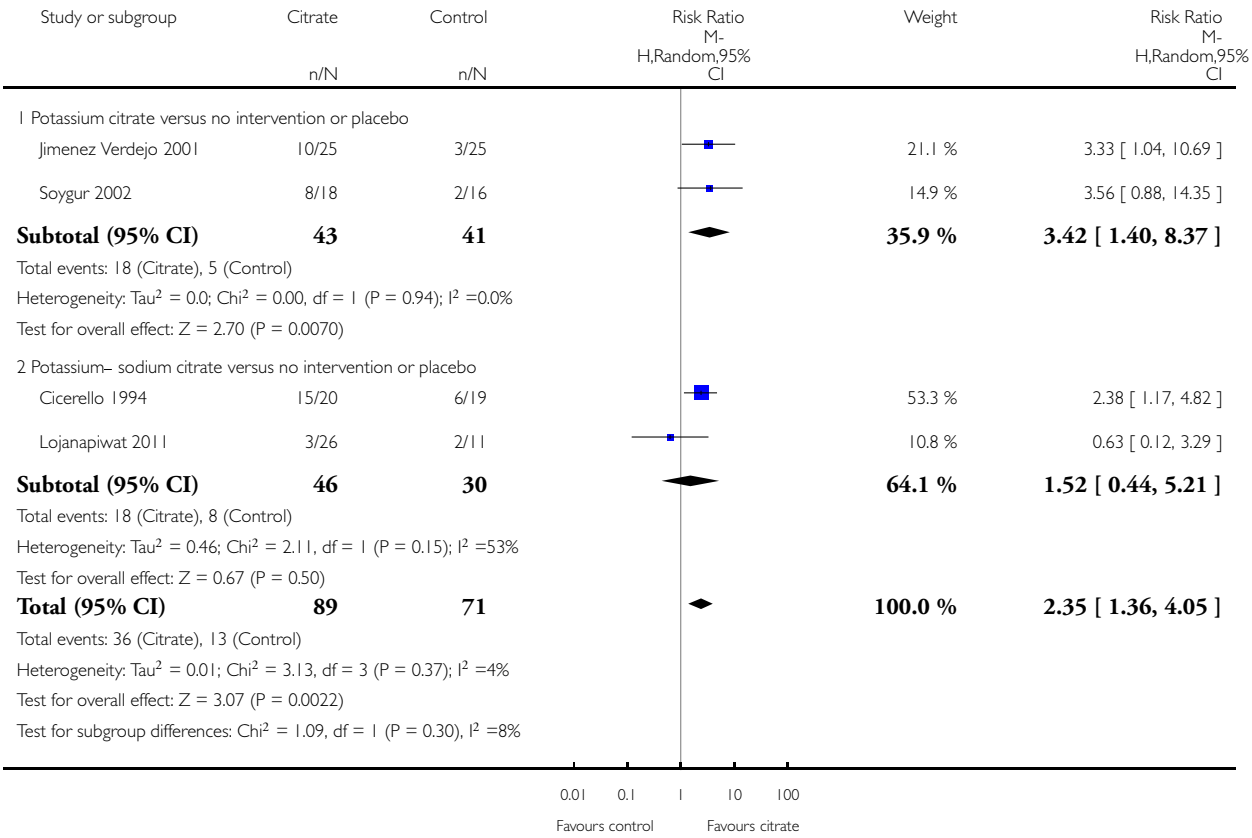
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reduction in stone size	4	160	Risk Ratio (M-H, Random, 95% CI)	2.35 [1.36, 4.05]
1.1 Potassium citrate versus no intervention or placebo	2	84	Risk Ratio (M-H, Random, 95% CI)	3.42 [1.40, 8.37]
1.2 Potassium-sodium citrate versus no intervention or placebo	2	76	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.44, 5.21]
2 New stone formation	7	324	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.10, 0.68]
2.1 Potassium citrate versus no intervention or placebo	3	144	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.11, 0.64]
2.2 Potassium-magnesium citrate versus no intervention or placebo	1	64	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.08, 0.52]
2.3 Potassium-sodium citrate versus no intervention or placebo	3	116	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.03, 2.63]
3 Stone size stability	4	160	Risk Ratio (M-H, Random, 95% CI)	1.97 [1.19, 3.26]
3.1 Potassium citrate versus no intervention or placebo	2	84	Risk Ratio (M-H, Random, 95% CI)	2.19 [1.19, 4.02]
3.2 Potassium-sodium citrate versus no intervention or placebo	2	76	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.55, 4.51]
4 Urinary citrate levels	3	179	Mean Difference (IV, Random, 95% CI)	192.77 [108.19, 277.35]
4.1 Potassium-magnesium citrate versus no intervention or placebo	1	64	Mean Difference (IV, Random, 95% CI)	221.00 [84.90, 357.10]
4.2 Potassium-sodium citrate versus no intervention or placebo	2	115	Mean Difference (IV, Random, 95% CI)	176.69 [42.51, 310.86]
5 Adverse events	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Upper gastrointestinal symptoms	4	271	Risk Ratio (M-H, Random, 95% CI)	2.55 [0.71, 9.16]
5.2 Rash	1	64	Risk Ratio (M-H, Random, 95% CI)	3.19 [0.13, 75.43]
6 Dropouts	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Non-compliance	5	311	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.72, 1.99]
6.2 Adverse events	4	271	Risk Ratio (M-H, Random, 95% CI)	4.45 [1.28, 15.50]
7 Retreatment	2	157	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.06, 0.89]

Analysis 1.1. Comparison 1 Citrate salts versus placebo or no intervention, Outcome 1 Reduction in stone size.

Review: Citrate salts for preventing and treating calcium containing kidney stones in adults

Comparison: 1 Citrate salts versus placebo or no intervention

Outcome: 1 Reduction in stone size



Analysis 1.2. Comparison 1 Citrate salts versus placebo or no intervention, Outcome 2 New stone formation.

Review: Citrate salts for preventing and treating calcium containing kidney stones in adults

Comparison: 1 Citrate salts versus placebo or no intervention

Outcome: 2 New stone formation

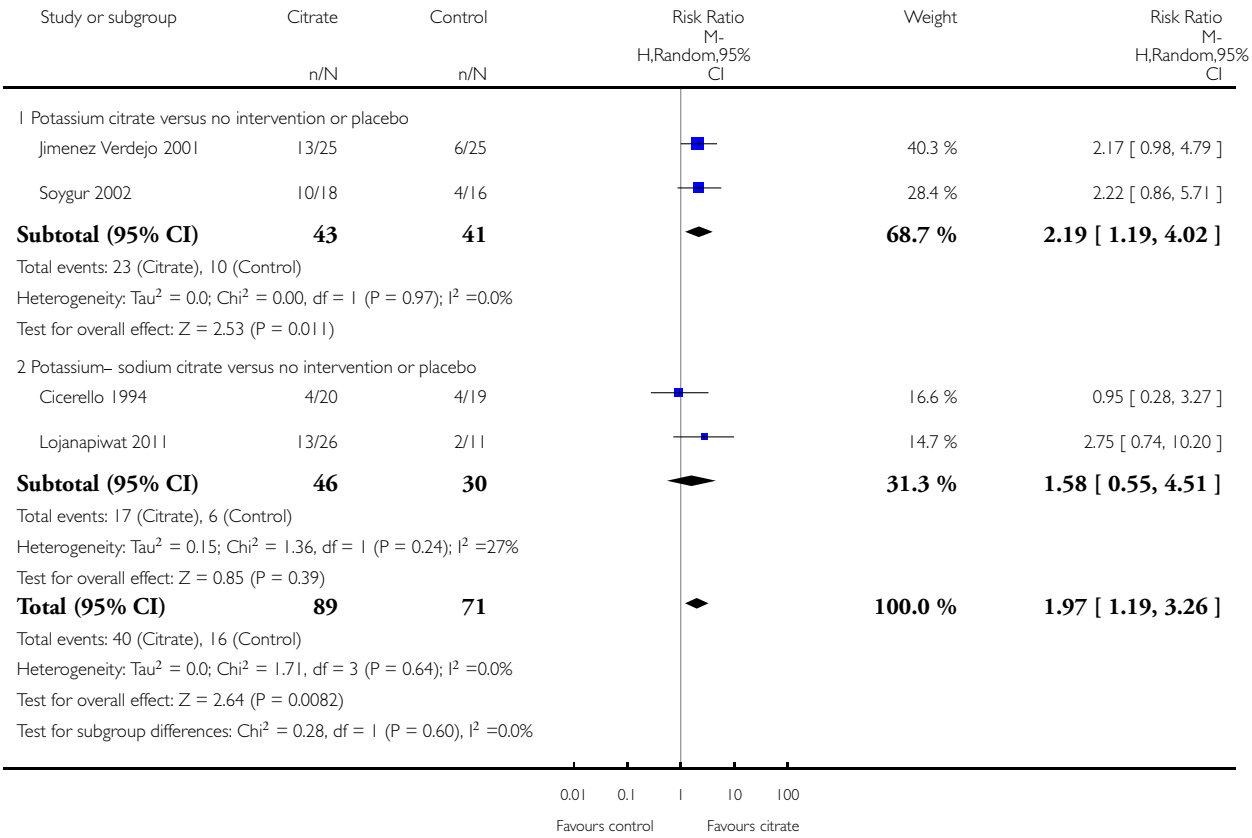
Study or subgroup	Citrate n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Potassium citrate versus no intervention or placebo					
Barcelo 1993	5/18	14/20		19.0 %	0.40 [0.18, 0.88]
Jimenez Verdejo 2001	2/25	11/25		15.0 %	0.18 [0.04, 0.74]
Soygur 2002	0/28	8/28		7.7 %	0.06 [0.00, 0.97]
Subtotal (95% CI)	**71**	**73**		**41.7 %**	**0.26 [0.11, 0.64]**
Total events: 7 (Citrate), 33 (Control)					
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 2.69$, df = 2 (P = 0.26); $I^2 = 26\%$					
Test for overall effect: Z = 2.92 (P = 0.0035)					
2 Potassium-magnesium citrate versus no intervention or placebo					
Ettinger 1997	4/31	21/33		18.1 %	0.20 [0.08, 0.52]
Subtotal (95% CI)	**31**	**33**		**18.1 %**	**0.20 [0.08, 0.52]**
Total events: 4 (Citrate), 21 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.29 (P = 0.0010)					
3 Potassium– sodium citrate versus no intervention or placebo					
Cicerello 1994	0/20	6/19		7.6 %	0.07 [0.00, 1.22]
Hofbauer 1994	11/16	16/22		21.0 %	0.95 [0.62, 1.44]
Lojanapiwat 2011	1/13	11/26		11.6 %	0.18 [0.03, 1.26]
Subtotal (95% CI)	**49**	**67**		**40.3 %**	**0.29 [0.03, 2.63]**
Total events: 12 (Citrate), 33 (Control)					
Heterogeneity: $Tau^2 = 2.94$; $Chi^2 = 10.44$, df = 2 (P = 0.01); $I^2 = 81\%$					
Test for overall effect: Z = 1.10 (P = 0.27)					
Total (95% CI)	**151**	**173**		**100.0 %**	**0.26 [0.10, 0.68]**
Total events: 23 (Citrate), 87 (Control)					
Heterogeneity: $Tau^2 = 1.10$; $Chi^2 = 29.40$, df = 6 (P = 0.00005); $I^2 = 80\%$					
Test for overall effect: Z = 2.74 (P = 0.0062)					
Test for subgroup differences: $Chi^2 = 0.18$, df = 2 (P = 0.91), $I^2 = 0.0\%$					

Analysis 1.3. Comparison 1 Citrate salts versus placebo or no intervention, Outcome 3 Stone size stability.

Review: Citrate salts for preventing and treating calcium containing kidney stones in adults

Comparison: 1 Citrate salts versus placebo or no intervention

Outcome: 3 Stone size stability



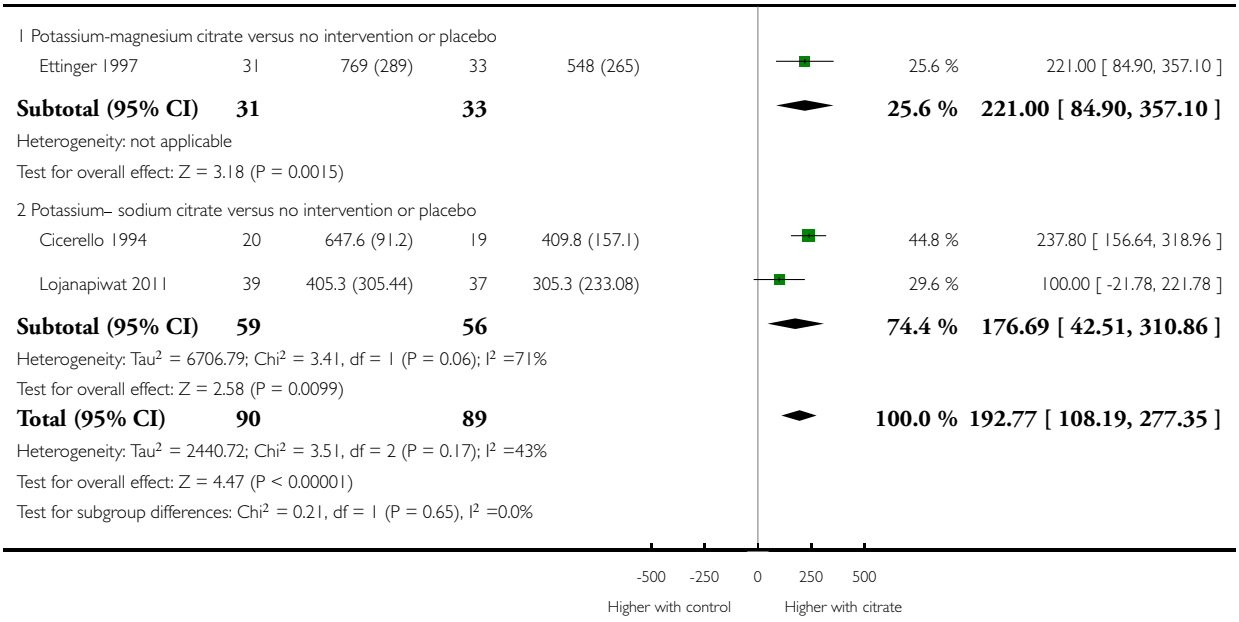
Analysis 1.4. Comparison 1 Citrate salts versus placebo or no intervention, Outcome 4 Urinary citrate levels.

Review: Citrate salts for preventing and treating calcium containing kidney stones in adults

Comparison: 1 Citrate salts versus placebo or no intervention

Outcome: 4 Urinary citrate levels

Study or subgroup	Citrate N	Mean(SD)[mg/d]	Control N	Mean(SD)[mg/d]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Potassium-magnesium citrate versus no intervention or placebo							
Ettinger 1997	31	769 (289)	33	548 (265)		25.6 %	221.00 [84.90, 357.10]
Subtotal (95% CI)	**31**		**33**			**25.6 %**	**221.00 [84.90, 357.10]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.18 (P = 0.0015)							
2 Potassium– sodium citrate versus no intervention or placebo							
Cicerello 1994	20	647.6 (91.2)	19	409.8 (157.1)		44.8 %	237.80 [156.64, 318.96]
Lojanapiwat 2011	39	405.3 (305.44)	37	305.3 (233.08)		29.6 %	100.00 [-21.78, 221.78]
Subtotal (95% CI)	**59**		**56**			**74.4 %**	**176.69 [42.51, 310.86]**
Heterogeneity: Tau^2 = 6706.79; Chi^2 = 3.41, df = 1 (P = 0.06); I^2 =71%							
Test for overall effect: Z = 2.58 (P = 0.0099)							
Total (95% CI)	**90**		**89**			**100.0 %**	**192.77 [108.19, 277.35]**
Heterogeneity: Tau^2 = 2440.72; Chi^2 = 3.51, df = 2 (P = 0.17); I^2 =43%							
Test for overall effect: Z = 4.47 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.21, df = 1 (P = 0.65), I^2 =0.0%							

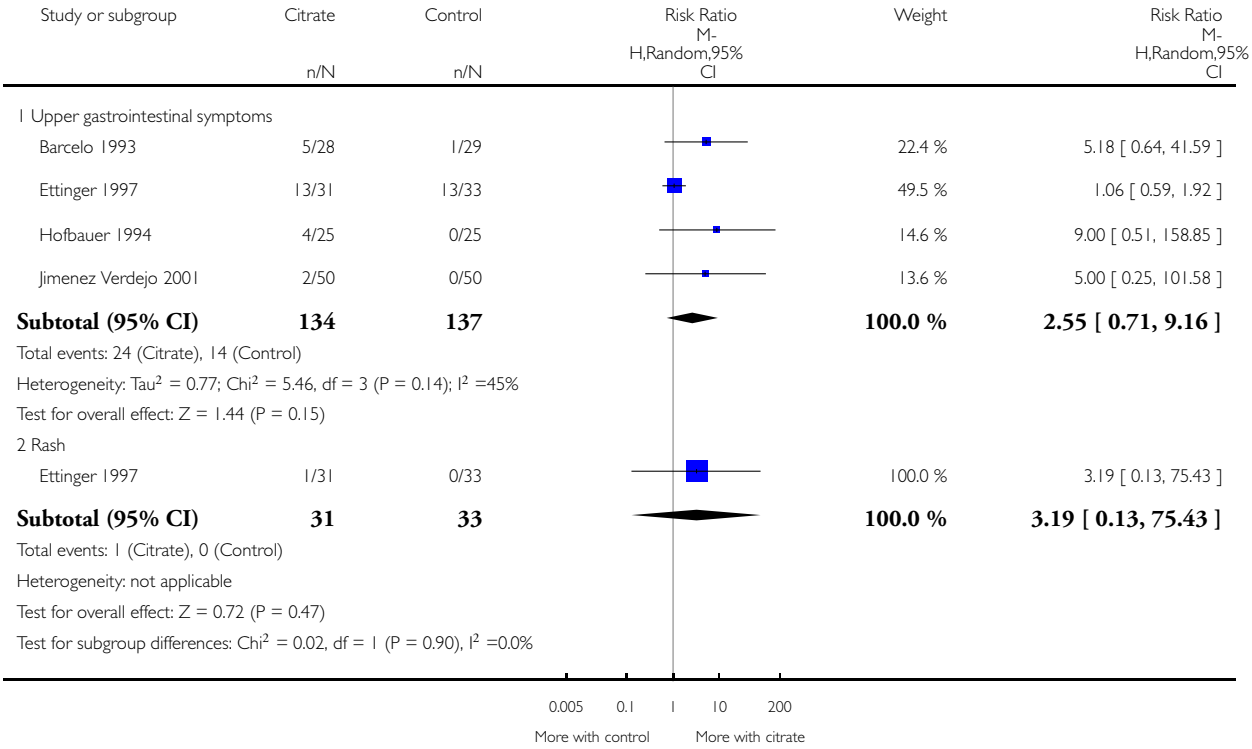


Analysis 1.5. Comparison 1 Citrate salts versus placebo or no intervention, Outcome 5 Adverse events.

Review: Citrate salts for preventing and treating calcium containing kidney stones in adults

Comparison: 1 Citrate salts versus placebo or no intervention

Outcome: 5 Adverse events

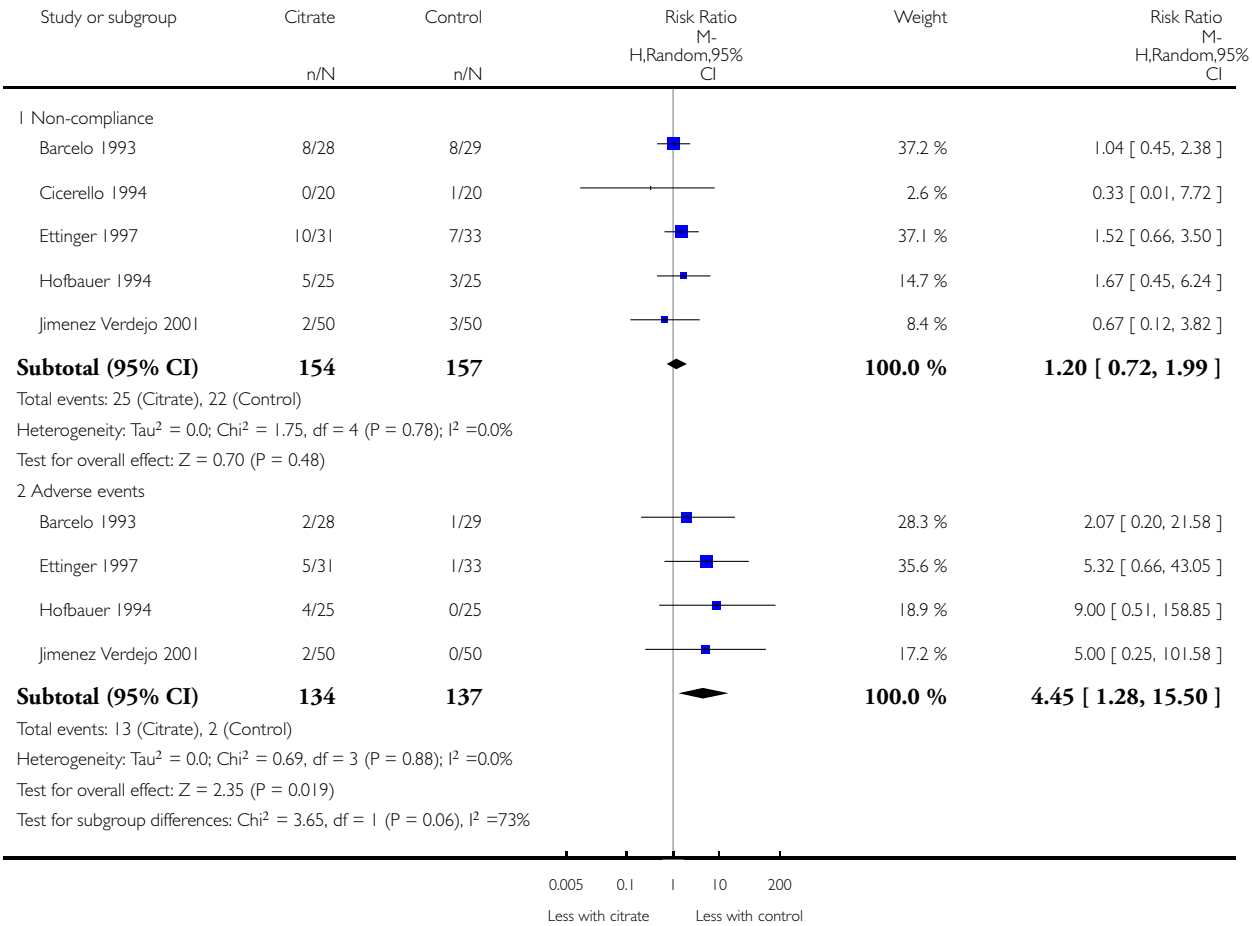


Analysis 1.6. Comparison 1 Citrate salts versus placebo or no intervention, Outcome 6 Dropouts.

Review: Citrate salts for preventing and treating calcium containing kidney stones in adults

Comparison: 1 Citrate salts versus placebo or no intervention

Outcome: 6 Dropouts

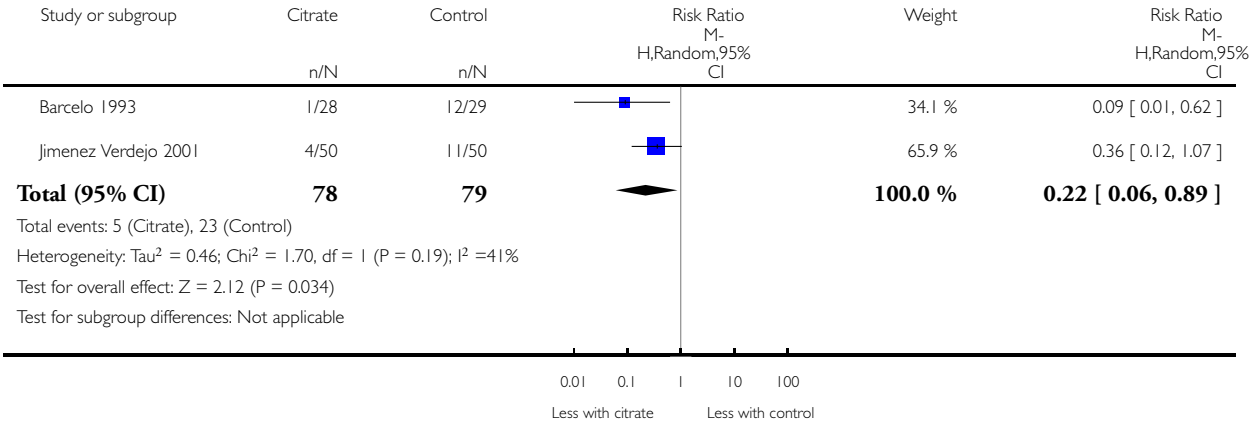


Analysis 1.7. Comparison 1 Citrate salts versus placebo or no intervention, Outcome 7 Retreatment.

Review: Citrate salts for preventing and treating calcium containing kidney stones in adults

Comparison: 1 Citrate salts versus placebo or no intervention

Outcome: 7 Retreatment



ADDITIONAL TABLES

Table 1. Adverse events

Study	Dropouts due to non-compliance	Dropouts due to adverse events	Side effects	Re-treatment
Barcelo 1993	Treatment: 8 Control: 8	Treatment: GI symptoms (2) Control: GI symptoms (1)	Treatment: minor GI symptoms (3) Control: no events	Treatment: ESWL (1) Control: ESWL (10), basket removal (1), open removal (1)
Cicerello 1994	Treatment: 0 Control: 0	Not reported	Not reported	Not reported
Ettinger 1997	Treatment: 10 Control: 7	Treatment: gas/bloating/nausea (3), difficulty swallowing (1), skin rash (1) Control: difficulty swallowing (1)	11% of all subjects had difficulty swallowing; 41.9% citrate and 39.4% control had new or worsening GI symptoms; 11.5% citrate had diarrhoea (one patient reported multiple episodes)	Not reported

Table 1. Adverse events (*Continued*)

Hofbauer 1994	Treatment: 5 Control: 3	Treatment: GI symptoms (4) Control: 0	Treatment: stomach pain, mild diarrhoea, nausea (4) Control: no events	Not reported
Jimenez Verdejo 2001	Treatment: 2 Control: 3	Treatment: GI symptoms (2) Control: 0	Not reported	Treatment: ESWL (4) Control: ESWL (11)
Lojanapiwat 2011	4 (group not reported)	Not reported	Not reported	Not reported
Soygur 2002	14 (group not reported)	Epigastric discomfort (6) (group not reported)	Not reported	Not reported

ESWL - extracorporeal shock wave lithotripsy; GI - gastrointestinal

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor Citrates explode all trees 2. ((potassium or sodium or calcium) and citrate*):ti,ab,kw in Clinical Trials 3. (isocitrate*):ti,ab,kw in Clinical Trials 4. (citric acid*):ti,ab,kw in Clinical Trials 5. (1 OR 2 OR 3 OR 4) 6. MeSH descriptor Urolithiasis explode all trees 7. (nephrolithiasis* or urolithiasis* or lithiasis*):ti,ab,kw in Clinical Trials 8. ((stone* or calcul*) and (renal or kidney* or urin* or ureter*)):ti,ab,kw in Clinical Trials 9. (6 OR 7 OR 8) 10. (5 AND 9)
MEDLINE	1. exp Citrates/ 2. ((potassium or sodium or calcium) and citrate$).tw. 3. isocitrate$.tw. 4. citric acid$.tw. 5. or/1-4 6. exp Urolithiasis/ 7. nephrolithiasis.tw.or urolithiasis.tw or lithiasis.tw 8. ((stone$ or calcul$) and (renal or kidney$ or urin$ or ureter*)).tw

(*Continued*)

	9. or/6-8 10. and/5,9
EMBASE	1. citric acid/ 2. ((potassium or sodium or calcium) and citrate$).tw. 3. isocitrate$.tw. 4. citric acid$.tw. 5. or/1-4 6. exp Urolithiasis/ 7. nephrolithiasis.tw. or urolithiasis.tw or lithiasis.tw 8. ((stone$ or calcul$) and (renal or kidney$ or urin$ or ureter*)).tw. 9. or/6-8 10. and/5,9

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random)
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention
	Unclear: Insufficient information about the sequence generation process to permit judgement
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes)
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed

(*Continued*)

	procedure
	Unclear: Randomisation stated but no information on method used is available
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with

(*Continued*)

	observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: VH, AM, BS, GN, CSB
2. Study selection: Cochrane team, RP, VH, CSB
3. Extract data from studies: VH, RP, CSB
4. Enter data into RevMan: RP, VH, CSB
5. Carry out the analysis: RP, VH, CSB
6. Interpret the analysis: RP,VH, AM, BS, GN, CSB
7. Draft the final review: RP, VH AM, BS, GN, CSB
8. Disagreement resolution: VH, RP, AM, BS, GN, CSB
9. Update the review: VH, RP, AM, BS, GN, CSB

Dr Rebecca Phillips and Mr Vishwanath Hanchanale contributed equally to this review, and are duly acknowledged as joint lead authors.

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The inclusion criteria in our protocol was patients aged 18 and over. During the review process, we came across a RCT by Cicerello 1994. This is an important study which we felt should be included therefore our inclusion criteria were changed to include patients aged 16 years and over.

NOTES

Dr Rebecca Phillips and Mr Vishwanath Hanchanale contributed equally to this review, and are duly acknowledged as joint lead authors.

INDEX TERMS

Medical Subject Headings (MeSH)

Calcium Oxalate; Calcium Phosphates; Citrates [adverse effects; *therapeutic use; urine]; Drug Combinations; Kidney Calculi [*chemistry; prevention & control; *therapy]; Magnesium Compounds [therapeutic use]; Potassium Compounds [therapeutic use]; Randomized Controlled Trials as Topic; Recurrence; Secondary Prevention

MeSH check words

Adult; Humans